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NATIONAL PURPOSE: HEALTH THROUGH SCIENCE

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INTRODUCTION

Throughout human history, disease, diability, suffering, and premature death have been relentless and implacable scourges of mankind. Attenuation of their impact has occurred only through the application of new knowledge gained through observation and research. Medical science, in the modern sense of the word, is less than 100 years old. Since the modern epoch began with the trail-blazing work of Pasteur, Koch, Ehrlich, and the other great pioneers in the late 19th century, the pace of discovery has been increasing. The past quarter century has been particularly fruitful.

Society's expectation from research in the biomedical sciences is the solution or amelioration of problems that threaten life and health. While modern medical science has made tremendous progress, tremendous problems remain--problems that tragically limit personal fulfillment and achievement.

The direct cost of disease, almost $70 billion per year, represents only the most visible expense. Indirect costs, judged by measures such as lost productivity, are enormous and yet fail to tally the serious psychological and social costs of illness to individuals and their families.

In the last decade or two, public attention has become intensively focused on serious problems concerning the quality, accessibility, and costs of health care, the financing mechanisms, and the availability of health manpower and facilities. In too much of the public discussion and debate on these subjects, sight has been lost of the fact that, whatever the system, delivery capability is at best only as good as the current state of knowledge. The latter is completely determined, and limited, by the effectiveness of past research efforts. The ultimate requirement--whether the objective is to provide better care for more sick people or to reduce the demand for health services by the eradication and prevention of disease--is new knowledge gained through scientific research.

Direction of research toward certain objectives does not automatically result in attainment of those objectives. Research is a complex activity that must be viewed in terms of the individuals who perform it, the institutional settings in which they work, and the resources available for the task.

Investigators select problems for a wide variety of reasons. Important elements include perception of scientific opportunity and sensitivity to priorities among problems in need of solution. Some investigators are oriented strongly to basic disciplines--genetics, microbiology, biochemistry; some tend to work at the interfaces between disciplines; while others devote their careers, or large portions thereof, to research in specific diseases, such as cancer. Direction of biomedical research involves an appreciation of these various talents and interests and some intuition as to the proper mixture needed to accelerate the development and application of advances in knowledge towards the prevention, cure, or control of disease.

Discoveries come in a variety of forms, from generalizable conclusions that illuminate large segments of biology and medicine to specific findings of narrow applicability. Interplay between these enable some creative scientists to discern universals in the mass of detailed data, and others to discover the applicability of broad principles to a specific problem area. Thus inductive and deductive processes lead to new and creative syntheses, theories, and applications.

The realization of society's expectations depends on the extent to which individual research workers, institutional research performers, and resource allocation processes can be

aligned with social goals. In the last quarter century, public policy in the United States has evolved decisively to forge machinery capable of converting society's expectations of biomedical research to reality. This has been achieved principally through steadily rising Federal support, the creation of a national network of scientific capabilities and institutional commitments, the development of the National Institutes of Health as the lead agency, and the organization of NIH research institutes oriented to broad health problem categories, such as child health, cancer, and heart disease.

The interplay of two factors--rising Federal support and award of funds on the basis of scientific excellence--has forged a national network of scientific capabilities and institutional commitments. This national system emerged as the consequence of decisions based upon independent appraisals of scientific and program priorities. Within the system, excellence is broadly diffused among hundreds of institutions and thousands of scientists linked in a common quest for new knowledge that will advance the health of the American people.

National expenditures for health research have increased from a token level of $87 million in 1947 to an estimated $2.7 billion in 1970--a growth rate of 16 percent a year. This growth has been paced by rising Federal investment in health research which grew at the rate of 20 percent a year,

mounting from $27 million in 1947 to $1.7 billion in 1970. Non-Federal expenditures grew more slowly--13 percent a year, from $60 million in 1947 to more than $1 billion in 1970. Both the national and the Federal research investment seek solutions to urgent health problems such as cancer, heart disease, mental illness, congenital abnormalities, family planning, child health, aging, and environmental pollution.

Scientists in government, industry, and the nonprofit sector--primarily academic institutions and medical schools--collaborate in the pursuit of health research objectives. Approximately two-thirds of all federally supported health research conducted outside federally owned laboratories and clinics is performed in academic institutions, principally in some 100 major medical centers situated in more than 40 States. Industrial organizations, which account for almost one-third of the Nation's expenditures for health research, are concerned primarily with the applied research vital to transforming new knowledge into new products. About five-sixths of the funds required to support such research are generated internally from the companies' own resources, with Federal contracts comprising the remaining one-sixth.

Public interest in health research has been dominated by a preoccupation with specific diseases that are highly visible, associated with high mortality rates, and often

characterized by prolonged suffering or disability. Reinforced by such dramatic developments as the prevention of polio and the successful treatment of tuberculosis and Parkinson's disease, medical research has gained strong public support since World War II--support predicated upon the clear expectation that research will ultimately lead to significant improvement in prevention, control, and therapy for the many health problems that still afflict mankind. The categorical research institutes of NIH give clear public visibility, and unequivocally manifest governmental concern with discovering the causes of disease and developing techniques for prevention and control.

The emergence of the Federal Government as the dominant source of support for biomedical research has imposed key responsibility for program balance upon Federal legislators and executives. Working in an environment of scientific and political constraints and pressure, these officials must constantly seek to optimize limited resources by achieving a balance among competing approaches to the solution of research problems. They must be continuously concerned, for example, with balancing the allocation of resources for: targeted versus untargeted research, basic versus applied research, and fields and disciplines versus categorical areas.

Until a critical mass of knowledge is developed, most scientists are convinced that support of a broad base of fundamental research conducted by the most competent investigators offers the highest probability of results beneficial to society, in both the long run and the short haul. When the critical mass exists (as it did in atomic physics upon initiation of the Manhattan Project), the achievement of results as quickly as possible is facilitated by allocating a larger share of resources to targeted research, to applied research, to specific categorical areas. There are competent scientists, however, who are persuaded that massive investment in important disease problems, no matter how limited the knowledge base, will lead to significant progress. A choice between these two points of view on rational grounds is not now possible, and decisions must be based on the professional judgment of scientists, administrators, and politicians. In practical and operational terms, all options tend to be exercised. Some share of the resources are allocated to high-risk research endeavors that are "targeted" (or "applied" or "categorical") because of the severity of the health problem, the physical and emotional suffering associated with it, and the high personal and social costs that even a slight increment in knowledge might substantially reduce.

ACCOMPLISHMENTS

A comprehensive survey of all significant recent additions to human knowledge by biomedical research would exceed the bounds of this report. Illustration of the contribution calls for selection. In the following discussion, an effort has been made to categorize progress in terms of major missions within the domain of health research. This is by no means the only criterion for selection that could have been chosen.

Two recent publications from the Committees on Research in the Life Sciences and on Science and Public Policy, of the National Academy of Sciences, entitled respectively "Biology and the Future of Man" and "The Life Sciences," have taken a somewhat different approach. Their primary focus is on the recent historical development of major themes of thought and streams of progress in the biological sciences, and selection was based on criteria for significance intrinsic to the field under review. The applicability of the new knowledge to human affairs in general and to human health in particular was a derivative rather than primary focus of those

analyses. The two approaches are complementary and mutually reinforcing. Moreover, the NAS publications are highly recommended, for they comprise elegent essays prepared by a group of the world's experts on an array of subjects.

The present review gives emphasis to those developments in categorical health-problem areas which seem to represent important milestones in the long and exciting history of man's assault on disease.

INFECTIOUS DISEASES, IMMUNOLOGY, AND ALLERGY

Historically, biomedical research scored its first successes in the control of diseases caused by infectious agents. First, the recognition of the route of transmission and the role of animal infections as reservoirs of human disease led to the sanitation of food and water, virtually eliminating the great plagues of typhoid fever, cholera, and bovine tuberculosis. Then came control of diseases that are carried from man to man by means of insects and other vectors, such as bubonic plague, typhus fever, yellow fever, and malaria.

The development of other remarkably effective immunizing agents, which have reduced the incidence of diseases transmitted by contact or by the respiratory route, such as smallpox,

diphtheria, and pertussis, is another important chapter in this history. Within the last two decades, vaccines for the prevention of poliomyelitis, measles, and rubella have been introduced into clinical practice. Poliomyelitis has been virtually eradicated from many countries; and there is every reason to believe that the waves of congenital anomalies--the very serious consequence of the mild or unseen rubella infection in expectant mothers--can be averted. Measles vaccines administered in mass-immunization programs have proved useful in reducing fatalities and other grave consequences.

These advances were possible because of the ability, as methodology developed, to identify the causative organism of a disease, to cultivate it in the laboratory and learn its characteristics, and then to prepare vaccines from it or from toxins it produces. The more recent advances in viral diseases such as polio, measles, and rubella derive from the techniques of tissue culture, which has transformed the field of virology.

It is not only the method of growing viruses in tissue culture that has accelerated virological research to its present state, at which some 350 agents of disease are known. Progress in virology exemplifies the irregular rate at which a discipline or a body of knowledge develops and the tangents along which its interests move. This is a result of the

interaction with other disciplines, the sophistication of its techniques and equipment, and the inventiveness of its concepts. A great thrust of the 1950's and '60's was the identification of new viruses, made possible by the discovery of immunofluorescence techniques, and by advances in serologic procedures and other means of tracing viruses. These have resulted in the discovery of "footsteps" of cancer viruses in tumor cells, even when the viruses themselves cannot be demonstrated, and the association of the Australian antigen with infectious hepatitis. The latter finding has just resulted in a practical technique for identifying Australian antigen in blood used for transfusion, thus providing a means for eliminating at least some of the sources of serum hepatitis.

The contributions of virology to the development of knowledge in other disciplines have also been manifold. Studies of the transformation of bacterial cells by their own viruses, the bacteriophages, have contributed enormously to the basis of molecular biology and to the conceptualization of the possible events involved in the change from normal to tumor cell. These accomplishments have derived from research on virus structure and chemistry and from the techniques of enzymology worked out in other disciplines. Investigation of central nervous system lesions found in victims of various degenerative nervous diseases has led to the demonstration of their viral causation in animals, suggesting the possible implication

of so-called "slow" viruses in such diseases as multiple sclerosis.

Immunology, in addition to illuminating areas of virology, has also contributed to other aspects of microbiology, to the understanding of pathology in various disorders, and to tissue transplantation and allergy. Immunochemical studies have clarified the structure and function of various classes of immunoglobulins, the blood substances that serve as defense against invading microorganisms and other materials foreign to the body. Studies on cellular reactions and mechanisms have shed light on tissue graft rejection and on how the body distinguishes its own "self" tissue from "non-self" tissue, as well as how it monitors constantly to detect and destroy abnormal self-tissue arising from genetic modification. Immunologic methods have resulted in the identification of many minor antigens in blood, have facilitated more accurate cross-matching, and have reduced the hazards of a mismatched blood transfusion due to repeated exposure to minor blood cell antigens. They have also resulted in the recent development and licensing of antibody which can prevent erythroblastosis fetalis due to Rh incompatibility between a mother and her unborn or just-born infant. Allergic disease phenomena are just beginning to yield to new techniques in immunology.

These techniques have made possible the confirmation of suspicions, based on observations of diseased tissue, that the immune mechanism of the body sometimes works against it, resulting in so-called auto-immune diseases. It can be expected that more work along these lines will elucidate the relation between previous acute infection and the insidious course of various chronic degenerative diseases, such as those of the central nervous system and of the skeletal and supporting tissues.

The phenomenon of cellular resistance to viruses and other parasites that reside within cells has been partly explained through investigation of interferon, a substance found within infected cells that prevents further proliferation of the parasitic agent. Interferon production and action are under intensive study. Such work may lead to techniques for protecting against the many viruses capable of producing either acute diseases or the changes in the genetic mechanism of cells which proceed to tumor formation.

Treatment of infectious diseases was revolutionized in the 1930's by the development of the sulfa drugs. This was followed in the 1940's and through the last two decades by the truly remarkable development of antibiotics that have brought most bacterial diseases under control. The methodology for drug development has been exploited in the search

for antitumor agents. Immunosuppressive drugs are now available to treat and maintain patients with intractable diseases such as lupus erythematosis, psoriasis, thrombocytopenic purpura, and certain types of granulomas, and to prevent rejection of transplanted organs or tissues. These practical uses encourage the hope that drugs will eventually be developed to block an allergic reaction or tissue rejection specifically without adversely affecting the entire immune mechanism.

METABOLIC AND RHEUMATIC DISEASES

Rheumatic diseases, such as rheumatoid arthritis, osteoarthritis, and gout, have yielded significant ground to intensified research. Although the cause of rheumatoid arthritis is still unknown, improved methods of diagnosis, a new generation of modern drugs, and more effective methods of physical therapy now prevent much crippling and keep most patients more productive and comfortable. Patients with osteoarthritis, the joint degeneration characteristic of old age, can also be maintained with greater comfort, and in many advanced cases new methods of joint and prosthetic surgery give relief. The cause and mechanisms of another classical crippling disease, gout, have been clarified. Improved methods of diagnosis and highly effective drug therapy are now available. From knowledge developed within the last 15 years, this

hereditary metabolic disease can be one of the best managed of man's serious disorders, and patients can lead normal and productive lives without fear of painful attacks and serious long-term joint and kidney complications.

Diabetes is the best known of the many metabolic diseases that have become more prominent in recent years as modern biomedical science has progressively subdued infectious disorders. Juvenile diabetes, once an invariably fatal disease, can now be controlled to the point where its victims can lead near-normal productive lives, though their life span is still much shortened. The nine-tenths of diabetic patients whose disease emerges during maturity need no longer be significantly handicapped, thanks to a spectrum of modalities of management, from simple weight reduction to insulin replacement.

Research advances in other metabolic diseases, like cystic fibrosis and PKU (phenylketonuria), many of them recently discovered, concern largely their recognition and the elucidation of their causes. Even here, however, as exemplified by galactosemia (which once led to mental retardation and early death) or Wilson's disease (with its formerly progressive organ and brain damage), effective diet and drug therapies now ensure normal development and function, provided the diagnosis is made early and treatment promptly instituted.

Through knowledge gained over the past decade or two, genetic counselling based on the scientific recognition of traits for known hereditary diseases in prospective parents has become feasible. In addition, the presence (or absence) of many genetic disorders in the unborn fetus can be ascertained through the new technique of amniocentesis--extraction of a sample of amniotic fluid--and subsequent examination of fetal cells. This advance is significant to families "at risk" for a hereditary disease, as it is now possible to determine prior to birth whether the fetus has chromosomal defects and to rule out the presence of over 30 metabolic abnormalities. When fetal disease is diagnosed, a pregnancy that would otherwise lead to certain disaster can be terminated. On the other hand, therapy can often be administered before and immediately after birth, saving lives and preventing damage to the brain. Moreover, the new technique enables the family to attempt to have children, assured that a suspected metabolic disease can be ruled in or out prenatally.

The achievements of research in endocrinology and endocrine disorders during the last two decades have been impressive. Thanks to these advances, severe symptoms of the menopause can be ameliorated; thyroid abnormalities, diagnosed and treated promptly and effectively; and hormonal deficiencies such as Addison's disease and certain types of dwarfism, recognized and corrected through specific replacement therapy.

Equally important, isolation of various hormones and recognition of their respective roles have made possible reasonably effective control over human fertility. This permits not only elective planning and limitation of offspring for medical, personal, or social reasons, but also the establishment of fertility in many women who were previously unable to have children.

The last two decades have seen a gratifying expansion of knowledge concerning the function of the gastrointestinal tract and associated organs--the liver, gallbladder, and pancreas. Advances have been made in surgery for serious digestive disease and in the medical management of disorders like peptic ulcer and ulcerative colitis. The virus responsible for serum hepatitis, and increasingly important health problem in the United States, has been recognized, and methods have been developed for detecting the organism in blood collected for transfusions.

In the area of blood disorders, prevention and effective treatment of refractory bleeding in hemophilia has become possible. Previously life-threatening dental extractions and even major surgery can now be carried out in patients who have the bleeding trait. Research on sickle cell anemia, another serious hereditary blood disorder, has clarified the

basic mechanism of blood cell sickling, and experimental methods for the treatment of acute sickling crises are under investigation.

The last decade has seen the emergence of two new life-saving and maintaining treatment methods for patients with irreversible kidney failure, namely dialysis with artificial kidneys and kidney transplantation. New drugs now permit effective treatment of kidney infections that once had a grave prognosis, and advances in the fields of urology and urologic surgery permit the repair of congenital anomalies and other corrective steps never before attempted.

HEART DISEASE

During the past 25 years, research on the cardiovascular system--which includes closely related aspects of the kidneys and lungs as well as the heart, arteries, and veins--has produced major progress in three directions. The first of these was in the diagnosis and reconstruction of congenital and acquired abnormalities of the heart and vessels. The second was in knowledge of the basic mechanisms governing the heart's muscular function and rhythm, of salt and water metabolism, and of the autonomic nervous system, including vastly improved pharmacologic control of these factors as they relate to

circulatory disease. The third thrust of research was in acquiring information essential to the understanding and prevention of atherosclerosis and hypertension, now the two major causes of premature death and disability among Americans. Similar epidemiologic data were acquired relative to chronic obstructive pulmonary disease.

Treatment of Congenital and Acquired Heart Disease

One of the more dramatic achievements of research has been the development of cardiopulmonary bypass. This technique, which permits the heart to be stopped and opened for six hours or more, has given rise to two decades of progress in surgery. Valves damaged by rheumatic or congenital disease can be replaced by prosthetic substitutes or by valves from human cadavers or animals. There remain few congenital malformations that are neither curable nor alleviated by reconstructive surgery. In the last several years, bypass of isolated lesions in arteries has reached a fine art. Most recently, lesions in the coronary vessels have also become correctable. Patients with angina and even acute myocardial infarction, previously considered beyond surgical relief, have been helped.

These achievements have been made possible by comparable advances in diagnostic methods. Prominent among these are

catherization of the heart, the detection of shunts by means of radioactive gases, and angiographic techniques that now permit visualization of the fine branches of the arterial tree supplying the heart itself. Such research has drastically altered the practice of cardiovascular medicine and rehabilitated scores of thousands who were previously doomed to disability or early death.

Control Mechanisms

During the past 10 to 20 years, there has been a marked decline in mortality from severe or malignant hypertension and from arrhythmias of the heart, especially as caused by myocardial infarction. There has also been a minor revolution in the medical management of severe heart failure. These favorable developments may be ascribed to studies that have provided access to some of the basic controls of the circulation. The biochemistry and metabolism of epinephrine and similar hormonal substances, of aldosterone, and of peptides acting on blood vessel tone have been illuminated by many workers and laboratories. The exposure of metabolic control points has allowed the development of new pharmacologic agents capable of altering these mechanisms with increasing precision and thus fewer untoward side effects. Similar research has brought forth several generations of new diuretic and antihypertensive agents. Treatment for congestive failure and

nearly all forms of hypertension has become much more practical, predictable, and effective.

The cause of most hypertension remains a mystery, but two forms have been discovered through exploration of the blood pressure altering effect of adrenal hormones and of deprivation of kidney blood supply. The diagnosis of such conditions has steadily improved. Cure remains surgical, but the rate of success has greatly increased.

The manner in which blood coagulates and saves life, or causes thrombosis, which threatens life, has been steadily clarified in past years. The place of anticoagulants in medical practice has become better understood, and use of fibrinolytic agents in such hazardous states as pulmonary embolism and coronary thrombosis is being explored.

The emergence of the coronary care unit as a prime adjunct to the modern hospital is due to the discovery of two drugs and the experimental development of two techniques within the last 20 years. The drugs are procaine amide and xylocaine; the techniques are electrical defibrillation and external cardiac massage. The combination of these, converted to routine therapy in the last five years, means that almost no hospitalized patient need ever again die of simple cardiac arrhythmia. The result should be a highly significant

effect on mortality from myocardial infarction and certain hazardous medical procedures including anesthesia.

Prevention

The least spectacular and most tedious research of the past two decades may in the long run have the most important impact on disability from cardiovascular and cardiopulmonary disease. This research has involved prospective study in which populations have been surveyed for certain features or variables and then watched as disease manifested itself.

The factors predisposing to coronary artery disease have been illuminated. These most prominently include hyperlipidemia, cigarette smoking, and hypertension. The information at hand provides a basis for experiments on the effects of manipulating each variable. Associated laboratory research has, moreover, provided insight into mechanisms controlling these variables. Statistics show that cessation of cigarette smoking decreases rather abruptly the risk of sudden (coronary) death. Hyperlipidemia has been differentiated into several specific forms, the genetic base separated partially from the cultural or environmental, and useful regimens for successful management developed. Field trials of drugs that reduce blood lipids have been set in motion, and a basis has been laid for trials of dietary changes capable of lowering cholesterol. A valuable

collection of population data relative to hypercholesterolemia, coronary disease, and strokes has been established.

Less complete data have been assembled relative to chronic obstructive pulmonary disease, which seems to be rapidly increasing in this and other industrialized societies. The latter studies are entering an accelerated phase. The last five years have seen the creation of membrane oxygenators capable of taking over the work of the lungs for days without significant damage to the blood. In addition to the promise of lending the surgeon more time for cardiac operations, this achievement may create a new impetus for lung research like that which the first bypass machines afforded heart research over 20 years ago.

NEUROLOGICAL AND SENSORY DISEASES

Through recently developed technology for unraveling the metabolic chemistry of the cell, a substantial number of familial neurological diseases have been identified as errors in metabolism. Identification of the enzyme defects causing Gaucher's, Niemann-Pick and Tay-Sachs diseases is illustrative. In fact, the specific defect in each of the six currently recognized disorders of lipid metabolism in the nerve cell has been pinpointed. Similar successes can be cited for the identification of errors in amino-acid and carbohydrate

metabolsim. As the tools for analysis and diagnosis increase in sophistication and power, many disorders previously classified under one entity are revealed to be two, three, or more different conditions, each usually requiring a specialized approach.

In some newly discovered disorders, such as those of lipid metabolism, cheap and rapid diagnostic tests have been devised. Muscle biopsy coupled to recently developed histochemical staining is being used to classify the numerous muscle diseases.

A major advance in the field of neurology has been the discovery that a group of devastating disorders, including kuru, Jacob-Creutzfeldt disease, and subacute sclerosing panencephalitis (SSPE), are infections involving viral-like agents distinguishable by a peculiarly long latency leading to a smoldering, ultimately fatal disease. For example, the agent for SSPE has been identified as the measles virus. The "slow virus" diseases are reproducibly transmissible from man to experimental animals, in which they are more amenable to study. There are good reasons to believe that similar agents could be involved in a number of diseases, neurological and otherwise.

The study of an abnormal condition requires an understanding of the corresponding normal condition. Disability

is usually associated with a defect of a chemical or physiological mechanism. A large archive of data has been accumulated on anatomical, physiological, and chemical aspects of almost every aspect of the nervous systems of man and many animals. Progress depends heavily on these essential data. Thus, as the molecular events in the nerve membrane are investigated by biophysicists, who have begun to understand the ionic basis for the nerve impulse, clinical investigators have applied the knowledge to neuromucular disease. Myasthenia gravis, is characterized by weakness of the muscles progressing usually to respiratory paralysis and death. Understanding of the neuromuscular junction suggested a successful approach employing inhibitors of the normal mechanisms that destroy the synaptic transmitter, acetylcholine. Many similar examples of help in correcting disease or disability through study of normal anatomy, physiology, or chemistry could be cited. A case in point is the striking result obtained in Parkinsonism with L-dopa therapy, which was tried because its importance for nerve impulse transmission in the central nervous system had been established in animals.

Stereotaxic surgery, so routine in present-day management of intractable pain, epilepsy, and formerly in Parksinsonism, is based on the results of extensive animal studies by many researchers interested primarily in how the nervous system works.

Deafness

Deafness is a common affliction of the aged. Studies by physiologists on the conduction and perception of sound have led to reliable techniques for measuring and testing auditory function. Clinically, a surgical procedure has been developed for mobilizing the stapes manually and correcting the ankylosis that was interfering with the transmission of sound. Many senior citizens are grateful for this relatively simple procedure.

Evoked-response audiometry, a recently discovered test, makes possible early detection of incipient deafness in the infant child. In view of the recently recognized importance of early hearing in the development of language, it is imperative to initiate corrective measures as early as possible.

Visual Disorders

Advances in the prevention, diagnosis, and treatment of visual disorders have made significant inroads against visual disability. With the marked decrease in prevalence and severity of some visual problems, there has been a shortening of hospitalization, a shift from inpatient to outpatient treatment, and a reduction in the numbers of patients requiring vocational rehabilitation or lifetime support.

Cataract surgery has been made safer, easier, and more successful by several technical improvements. These include advances in suture techniques, improved microscopic instrumentation, use of the enzyme alpha chymotrypsin, and development of a cryoprobe for removal of the lens. In children with congenital cataracts, useful vision has been preserved through earlier surgery employing the aspiration technique, followed by the fitting and use of corneal contact lenses. Experimental galactose cataracts, very similar to those found in diabetic patients, have been produced in rats. The fact that these opacities can be prevented medically suggests that further effort may lead to effective medical treatment of certain types of cataracts in humans.

The chances for successful corneal transplantation have increased considerably as a result of advances in operative technique. In certain degenerative conditions, success rates have climbed from 10 percent to more than 50 percent. A further increase should follow the recent development of methods to improve the viability of donor corneas.

The development of biological glues has led to the permanent mounting of contact lenses to improve vision in cases not responsive to conventional therapy, as well as to serve as a "blow-out patch" in perforation of the cornea. For refractive errors, soft, hydrophilic contact lenses, developed

over the last ten years and recently approved by the Food and Drug Administration, will offer improved vision to patients unable to tolerate conventional lenses. Also, the soft lenses are being tested for therapeutic use, as in the delivery of medication to the eye.

Open- and closed-angle glaucoma can now be rapidly and accurately differentiated by means of gonioscopy. The prevalence of closed-angle glaucoma, curable if detected early, has been reduced; and treatment of the open-angle type has been changed from surgical to medical through the introduction of systemic carbonic anhydrase inhibitors and topical adrenergic drugs, markedly decreasing morbidity. The earliest visual changes from glaucoma can now be detected by means of improved perimetric techniques. Recent emphasis has been on earlier detection before visual-field loss occurs. Steroid provocative testing, improved tonographic procedures, and studies of the hereditary pattern of glaucoma may make possible the identification of high-risk individuals for early treatment.

In the area of infectious diseases, several drugs have been found to exert a direct toxic effect on viruses *in vitro*. The most notable of these, idoxuridine (IDU), is used in the treatment of herpes simplex infections of the eye--the first successful clinical treatment of a viral disease. The number of children with visual disabilities due to the ocular

complications of rubella should sharply decrease as a result of the development and use of the rubella vaccine.

Success rates in surgery for retinal detachment have increased from 50 to 90 percent. This has resulted from the development of better diagnostic and operative techniques, especially through widespread use of the indirect ophthalmoscope and the use of scleral buckling in surgery. Cryopexy has proved to be a useful alternate surgical procedure, permitting shortened operating time and less trauma to the eye. The development of fluorescein angiography has led to greater understanding of pathology in various retinal disorders secondary to lesions in the choroid, and has aided in the precise location of such lesions prior to treatment. Widespread use of xenon arc and laser photocoagulation has permitted successful outpatient treatment of various retinal disorders, including retinal tears and degenerative conditions such as macular edema, that previously required hospitalization.

Identification of excessive oxygen levels as the cause of retrolental fibroplasia (RLF) in premature infants almost eliminated this blinding condition a decade ago. Following the recent increased use of high levels of oxygen for respiratory distress in the newborn (an estimated 40,000 cases per year), progress has been made in establishing guidelines for safe levels of arterial oxygen through monitoring to prevent

eye damage. The early work with RLF was particularly gratifying in terms of the economic and social aspects of the disease. An original expenditure of $50,000 for research offset the $120 million estimated as the cost of lifetime support for infants afflicted with the disease in just one year.

Fluorescent dyes and radioactive tracers now aid in diagnosing and detecting tumors of the eye. Improvements in chemotherapy, X-ray therapy, and radioactive implants have led to clinical trials with these methods as an alternative to enucleation.

Toxoplasmosis has been identified as a major cause of uveitis. Many of these cases respond well to treatment with pyrimethamine. Nematode invasion of the eye has been defined as a distinct entity primarily found in children. Progress has been made in the treatment of previously refractory cases of uveitis with antimetabolic and immunosuppressive drugs.

CANCER

Major advances in the understanding of cancer, as well as real progress in the management of patients with this group of diseases, have taken place in the last quarter century.

Carcinogenesis

The understanding of the role of extrinsic chemical and physical agents in the causation of neoplastic disease has been widely extended. By now about 1,000 chemicals have been shown to produce neoplasms in various animal species. Overwhelming evidence has accrued that approximately 30 environmental agents, including certain metals, ores, air pollutants, oils, and radiation are associated with increased cancer in exposed persons. This information has resulted in reduction of levels of exposure to many of these agents. The potentiality of compounds carcinogenic for animals to cause cancer in man constitutes a major issue confronting the field of environmental health.

Approximately 200,000 new chemical entities are introduced into the environment each year, and many of these in large amounts. The formulation of valid predictive hypotheses would greatly facilitate studies of chemical carcinogenesis. This will require knowledge of the mechanism whereby certain carcinogenic substances transform the DNA, the information and control system of the cell, as well as data on the absorption, fate, and excretion of such substances. Current progress in the disciplines of molecular biology and pharmacology-toxicology at least offers hope for the achievement of such predictive synthesis. Considerable data already

exist on the induction of tumors by viruses and radiant energy of various types. The phenomena are potentially interpretable in the light of knowledge of the molecular biology of the cell, although the specific lesion cannot yet be described in biochemical terms.

An enormous amount of evidence related to viral causation of cancer has accumulated. Over 120 viral agents have been shown capable of inducing cancer in experimental animals, and in a few cases vaccines have prevented such induction. The further investigation of viral carcinogenesis has been facilitated by dramatic parallel expansion in the understanding of energy and information transactions at cellular and molecular levels, through studies in genetics, molecular biology, molecular genetics, and protein and nucleic acid chemistry. This development affords a clearcut example of mutual reinforcement of disease-oriented and discipline-oriented scientific endeavors. In this connection, for instance, it has been shown that animal tumors can be produced by the nucleic acid core of a tumor-causing virus, and that viral genetic material is incorporated into the cellular genetic material of animals with virus-induced cancer.

Relevance of viral carcinogenesis in animals to cancer in man has been bolstered by evidence obtained through a number of lines of investigation. For example, particles

similar to the RNA virus particles involved in animal tumors have been found in human neoplastic disease. Particles resembling animal tumor viruses have been found in women with breast cancer and in human acute leukemias, lymphomas, and cancers of connective tissue (sarcomas). Herpes-type DNA viruses--especially one member of this group, the Epstein-Barr virus (EBV), considered by some workers as almost surely the major if not the only cause of infectious mononucleosis--have been associated with Burkitt's lymphoma, cancer of the postnasal tissues, cancer of the uterine cervix, and human chronic myeloid leukemia.

Recent insights arising from studies on viral carcinogenesis, on agents that are carcinogenic in combination but not alone (co-carcinogenesis), and on molecular organization and function of living materials have given rise to a number of theories about the causation of cancer. These may point the way to clarification of the nature of the abnormal processes in the cancer cell and thus provide leads to their prevention or reversal.

Diagnosis and Treatment

Research has provided methods for earlier diagnosis of cancer, especially by exfoliative cytology and by radiology. The combination of improved diagnostic and surgical procedures,

radiotherapy techniques, and post-treatment care--all resulting from new discoveries in research--have approximately doubled 5-year cure rates, from about 20 percent in the late 1930's to about 40 percent in the late 1960's. Under the heading of improved post-treatment care is a long list of major discoveries in the management of surgical shock, disorders of fluid and electrolyte physiology, postoperative infections, parenteral alimentation, disorders of blood coagulation, and other problems.

Once cancer has become disseminated throughout the body, or in the case of some forms of cancer such as leukemia and lymphoma in which dissemination begins early in the disease, surgery cannot be curative and radiation can cure in only a small percentage of cases. Major attention, therefore, has focused on the development of chemotherapeutic and immunologic methods that selectively destroy cancer tissues.

Chemotherapy. Cancer of specific types accounting for about 15 percent of all occurrences of the disease have proved responsive in some measure to chemotherapeutic agents. Susceptibility varies considerably. In diseases such as choriocarcinoma, Burkitt's lymphoma, and Hodgkin's disease, where the rate of tumor cell proliferation is rapid, as many as 70 percent of all patients in some studies appear to have been cured. The responsiveness in other types is lower.

Only about 20 percent of children with acute lymphatic leukemia are cured, but life expectancy for most is extended far beyond the 2- to 3-months survival common in the early 1950's.

The dramatic if limited advances in chemotherapy have provided a sound basis for further work. Major causes of therapeutic failure (for example, sequestration of cancer cells from therapeutic agents by a drug-impenetrable blood/brain barrier) have been identified. In meningeal leukemia, for instance, antileukemia drugs administered by the usual routes are not effective, but the outcome is much improved if the drug is delivered into the cerebrospinal fluid so that it can reach the tumor cells. Correlation of the drug-sensitivity of a tumor to the rate of cell proliferation also provides a clue to the nature of successful treatment where it has been attained. Those drugs now available destroy both normal and tumor cells that are in the process of synthesizing DNA. In acute lymphatic leukemia and other rapidly growing tumors, a high percentage of the tumor cells but only a small fraction of the normal "stem" cells that continually produce red blood cells or intestinal epithelium are in this stage at a given time. Thus, while the drugs destroy both tumor and normal DNA-synthesizing cells, the effect against the tumor cells is quantitatively much greater. Under optimal conditions the drugs destroy all the tumor cells, and normal cells develop from remaining stem cells that were not in the vulnerable stage during the treatment.

This also defines part of the problem of chemotherapy in the slower-growing tumors--the 85 percent of cancers that are not drug-sensitive. Here, the cells are not so synchronously involved in DNA-synthesis and division. Studies on the mechanisms of drug action may lead to agents that strike more specifically. There is a real hope that cure rates can be significantly improved in the sensitive cancers and a reasonable basis for further exploration of chemotherapeutic approaches in cancers that are relatively insensitive.

Radiation therapy. Research has extended significantly the range of applicability of radiation in the treatment of neoplastic diseases. Perhaps the most impressive gains have been reported for Hodgkin's disease, where radiation therapy has yielded cure rates of up to 50 percent of early cases.

DENTAL DISEASE

A scientific basis for water fluoridation as an effective caries-preventive measure has been established. The daily human intake of water containing 1 part per million of fluoride ion has been shown to reduce the incidence of tooth decay by as much as 60 percent, and this protective effect is now known to be mediated through changes in the molecular structure of the crystal components of tooth enamel.

Subsequent studies have greatly advanced understanding of the whole process of calcification, as well as the caries process itself. Utilization of special germ-free animal techniques has provided evidence that caries is indeed an infectious, transmissible disease resulting from specific microorganisms. These studies have also revealed that bacterial plaque deposits, produced by these organisms on the surface of the teeth, constitute the initial state in tooth decay. This has suggested the possibility of control through enzymatic, antibiotic, and antibacterial approaches.

Biomaterials research has led to the development of a plastic sealant to protect the chewing surfaces of children's teeth from decay. Another innovation is an adhesive material that bonds to the tooth for use in fillings. Another is effective, biologically compatible, synthetic tooth implants.

In disorders of growth and development, notably cleft lip and palate, research has improved diagnostic methods, rehabilitative surgical procedures, speech therapy, and more recently, psychological management.

In recent years, evidence of a role of both toxic and allergic factors in the causation of periodontal disease has emerged. Inflammation leading to tissue damage in the major form of periodontal disease appears to be an allergic response

to bacterial products. Bacterial plaque formation has again been shown to play a causal role. Another important discovery is that a tissue-destroying enzyme, collagenase, exists to some extent in normal gingival tissue and to a strikingly increased extent in patients with periodontal disease. The enzyme acts on collagen, the major protein of all connective tissue. Other notable contributions to basic knowledge include the discovery of a fiber (oxytalan) in connective tissue and the finding that defects in crosslinking patterns in collagen may strongly influence the tissue breakdown that occurs in periodontal disease. In epidemiologic studies a correlation between poor oral hygiene and periodontal disease has been established.

Among the other areas of oral research, one of the most promising is the study of the herpes simplex virus. Herpetic infections (fever blisters) affect the nose, lips, and oral tissues; and the herpes simplex virus has been implicated in nonepidemic viral encephalitis, skin disease, and genital and eye infections. Notable are recent findings related to the structure, chemical composition, and biosynthesis of the virus, and to information about virally induced pathology and the immune response to this infection. Studies suggest that even mild viral infections could trigger an auto-immune response that would make an individual allergic to one of his own proteins.

MENTAL HEALTH

Drug Therapy

Psychoactive drugs have helped reduce the Nation's mental hospital population, now less than half of what it would have been if the rising trend, reversed in 1955, had continued. The phenothiazines often control the symptoms of schizophrenia; antidepressants have virtually replaced electroshock in the treatment of depression; and lithium is highly useful against manic-depressive psychosis. Narcotic antagonists, which deprive the addict of satisfaction from heroin use, have been developed; and a synthetic opiate, methadone, has often proved effective in rehabilitating the heroin addict. L-dopa has been introduced as a rational and effective treatment for Parkinsonism.

New and Specialized Forms of Psychotherapy

Studies of interstaff and staff-patient interactions have led to the transformation of many mental hospitals from custodial to humanistic institutions. From these studies have come such advances as the *therapeutic community*, using *milieu therapy*, and the *day hospital*. *Behavior-shaping therapy*, stemming from basic learning research, has been used to alter

the behavior of hitherto untreatable psychotic and retarded children and of adults suffering disabling phobias. *Crisis intervention therapy* has reduced the need for hospitalizing many emotionally disturbed persons. And *group therapies* have permitted far greater numbers of patients to receive effective treatment. *Hypnosis*, now systematically explored in laboratory studies, often permits rapid treatment of symptoms that might otherwise consume years of psychotherapy. A new technique, *biofeedback*, is used to control physiological functions once considered totally involuntary. Instruments are employed to feed back to the patient signals of blood pressure, certain brainwaves, or the tension of muscles. The method is being applied successfully in ailments having a large psychological component, including colitis, tension headaches, and some aspects of heart trouble. From basic research on stimulus-response relationships have come the techniques of *programmed instruction*, a valued tool in re-training schizophrenics, rehabilitating brain-injured patients, and raising the intellectual level of the retarded.

Laboratory instruments now measure sensory thresholds, emotional and physiological reactions, perceptual distortion, and many other aspects of behavior. Such an array of procedures could become a huge "early warning system" to prevent developmental problems among millions of children with conditions that escape the usual examination.

Computerized clinical data, providing, for example, detailed daily assays of the patient's mood and behavior, make possible a closer observation of the hospitalized mentally ill. As one result, the exacerbation of symptoms can be anticipated and preventive or treatment measures instituted.

Childhood Environment and Later Development

Experiments with primates have yielded the first important corroborative scientific evidence that inadequate rearing does, in fact, disrupt normal behavioral development and lead to difficulties comparable to the personality disorders and severe mental illnesses encountered in humans.

Other studies with animals and human infants have shown that an infant's speed of development and later ability to handle stresses and problems are related to the amount and kind of stimulation in the first months of life. For lack of proper stimulation, children from low socioeconomic groups tend to develop a below-average level of intellectual functioning during the second year of life and to retain this deficit. Efforts to provide intellectual stimulation for infants from disadvantaged homes have succeeded in raising the IQ level significantly for at least a time.

Genetic vs. Environmental Factors in Mental Illness

Light has been thrown on the role of heredity in mental illness, and particularly on the biochemical processes controlled by hereditary factors which often seem to be involved. With respect to schizophrenia, most geneticists now hold that a predisposition to the disorder--not the disorder itself--may be inherited, and that it will lead to illness only in the presence of other factors, the most important of which seem to be certain parental attitudes and behavior.

HEALTH-RELATED BASIC RESEARCH

The direct attack on disease undertaken over the last several decades has been accompanied by a parallel research program in the basic biomedical sciences, designed to broaden understanding of life processes.

Information and Energy Transformations

No processes are more basic to the understanding of life in health and disease than those concerning the storage and transfer of information at the cellular and subcellular levels and the responses to that information in protein synthesis. The last two decades have witnessed a concerted effort to

clarify the nature of the process of transferring genetic information. Prior to 1945 it was known that chromosomes carry such information; that they contain DNA; that DNA, in minute amounts, could permanently change the nature of bacteria; and that a genetic defect could cause a specific biochemical defect within the body.

Events since 1945 have witnessed: affirmation of the "one-gene, one-enzyme" hypothesis--that the information determining the structure of each enzyme or protein is encoded within the DNA of the nucleus, and that each distinct chain of amino acids within an enzyme or protein is represented by a single gene; the description of the structure of DNA as a double helix; the first enzymatic synthesis of the nucleic acids, DNA and RNA; the demonstration that viruses contain nucleic acids that modify and regulate the metabolic processes of cells they infect; the deciphering of the genetic code and demonstration of its ubiquitous nature among all living forms; the discovery that information encoded within DNA is first transcribed into "messenger RNA" and then translated into the structure of protein through the action of "transfer RNA," which has a key role in the translation process; extensive studies of the structure of the particles within the cell called *ribosomes*, on which protein synthesis takes place; and discovery of the *sigma* and *rho* factors, which serve as signals as to which segments of the DNA are to be transcribed into

messenger RNA--factors which may have a key role in the processes of genetic regulation and control and in developmental biology.

Concurrent studies illuminated the extraordinarily critical role played by proteins in the functional anatomy of the cell. The proteins prior to 1945 were known as large macromolecules containing a variety of amino acids linked together in a complex structure and frequently having important catalytic or "enzymatic" functions in the conduct of the multitude of metabolic reactions carried on within the human body. Although many enzymatic reactions were known, only about 100 enzymes had been well characterized.

Since 1945 biochemical techniques have been developed which have made possible detailed studies of the structure of proteins. It has been shown that the linear sequence of amino acids within the peptide chain is determined by the sequence of nucleotides in the DNA of the synthesis-governing gene; and that a change in the nucleotide sequence of the DNA results in an altered structure of the protein being synthesized, elegantly exemplified by the altered structure of hemoglobin in sickle cell anemia. Detailed studies of the structure of enzymes have elucidated the precise nature of the "active site" where the chemical reactions initiated by the enzyme take place. Further descriptions of the many different enzymes

found in living systems have been completed, so that more than a thousand different enzymes have now been discovered and their specific roles as catalysts defined.

Extensive progress has been made in explaining energy utilization by cells for maintaining their integrity and performing external work. Particularly important was the demonstration of the centrality of high-energy phosphate bonds, as in ATP (adenosine triphosphate), as a source of energy for so many cellular processes--synthesis, secretion, contraction, electrical conduction, etc. In both animal and plant cells, function is intimately associated with the architecture of cell components as well as the utilization of energy from ATP. The chemical reactions involved in life processes, known only sketchily in the early 1940's, have now been extensively mapped. Primary controls, feedback loops, and transport phenomena--notably, the active transport of amino acids, sugars, and ions across the cell membrane--have been productively investigated. Innumerable enzymes have been isolated and related to their functions. And with the development of such techniques as tissues culture, ultracentrifugation, and paper chromatography, important information has been elicited on the structure, function, and composition of subcellular particles.

Prior to 1945, the cell was viewed as a liquid system of variable viscosity, separated from its environment by an

invisible membrane and containing a nucleus and several small bodies, or organelles, whose mysterious functions were just beginning to be explained. Since 1945 the application of the electron microscope to biological tissues, and the use of the ultracentrifuge and a wide variety of biochemical techniques for the separation and study of the various intracellular particles, have led to detailed examinations of the following: the *cell wall*, a complex biomolecular layer of lipid covered with protein on both the inner and outer surfaces and containing pores for the selective passage of amino acids, glucose, and other substances; the *cell nucleus*, and the nucleolus and chromosomes and other organelles within it, and the sequence of events through which they proceed during cell cycle and cell division; the *mitochondria* as a complex mechanism for the conversion and transfer of chemical energy from glucose to adenosine triphosphate; the *endoplasmic reticulum* as a membranous structure extending from the outer wall of the nucleus to the cell wall and apparently serving as a passageway to the outside for the proteins manufactured within the cell; the *ribosomes*, small particles--free or attached to the endoplasmic reticulum--which are the active sites of protein synthesis; the *lysosomes*, bodies containing enzymes that destroy proteins and nucleic acids within the cell--in essence, a system enabling the cell to "self-destruct" and to be removed if injured beyond repair; the *microtubules*, flexible, semi-rigid rods that form structural elements within

cells, within the tail of rat sperm, within the cilia that keep the air passages clear, and within the spindle that forms around the chromosomes during cell division; the *Golgi apparatus*, previously thought to be an artifact, but now known to play an important part in the secretion of enzymes, hormones, and other substances; and numerous other structures, such as myofibrils, neurofibrils, centrioles, and basal bodies, with specialized intracellular roles.

The Basic Nature of Disease

The dramatic explosion of knowledge in molecular biology is throwing much light on normal and pathologic states. The relationship of information and energy transformations at cellular and subcellular levels, together with the associated structural framework for these processes, relates directly to health and disease. Disease results from an altered structure and function of the cells within one or more organs and tissues of the body. Hereditary disease can be expressed within the cell by one of two routes: an altered genetic code, leading to altered protein structure, leading to altered cell function, leading to disease; or a failure of gene expression, leading to a deficiency of a given protein, leading to altered cell function and disease. Other types of disease can result from direct alteration of the structures of the cell through the action of chemicals, drugs, or bacterial and other biological

toxins; or from direct trauma, malnutrition, irradiation, or other external agents acting directly on cellular structures or the genetic apparatus. Aging is a process analogous, often intimately related to disease which is being studied by many of the newly available techniques.

Interaction of Man and Environment

While basic biomedical science may appear to be preoccupied with organs, cells, and molecules--more often than not in species other than man--its main objective is to enable man to function better in his environment.

The study of nutrition and metabolic processes has shed much light on the nature and role of essential dietary factors, such as vitamins and amino acids. Parallel advances in plant genetics and physiology and in pest control and crop cultivation joined with this knowledge to produce the "green revolution." New strains and hybrids of cereal grains are now cultivated in many parts of the world. Their use, along with dietary supplements derived from sources like fish and soybean, has begun to break open the vicious circle of malnutrition and mental deficiency caused by it. Adequate nutrition has been found particularly essential during the pre- and early postnatal period of life. Kwashiorkor can now be attributed with certainty to generalized protein deficiency, is known to be nonhereditary, and to be preventable and treatable through

proper nutrition. Several types of the malabsorption syndromes can be prevented by eliminations of certain foods from the diet.

One of the most difficult areas of biomedical research relates to the composition of man's environment and to his susceptibility and adjustment to the changes he has made in it. In addition to the increase in waste products from a growing population and a burgeoning industrial plant, thousands of new materials are synthesized annually, and many of these appear in intimate association with man's air, water, food, drugs, clothing, shelter, and transportation. No practical methods are available to assure the absolute safety of each of these substances--or, for that matter, of many materials that have long been in use. Extrapolation of their effects from animals to man is often extremely tenuous. Thalidomide, for example, can readily deform the human embryo, but similar effects are rarely seen in the rat. B-naphthylamine was suspected of causing bladder cancer in man long before it could be proved carcinogenic in an experimental animal.

New and sophisticated analytic procedures provide tools to identify and measure constituents of food, air, and water to a degree of sensitivity undreamed of only a few years ago. Many of these procedures are now automated, and computers facilitate both storage and analysis of the resulting data. Investigation of the use of therapeutic drugs over extended

periods poses especially difficult problems and occupies scientists in a variety of disciplines. Meanwhile, efforts are being made to design better and more economical drug screening tests. Advances in techniques for culturing human tissues and cells may eventually provide systems to replace many of the tedious and expensive tests in animals. In this general area of toxicology, scientists have come to realize that trade-offs and compromises must often be made, for all drugs possess some degree of toxicity. Today the science of drug design and use ranks with immunology and sanitation as one of the outstanding contributions of medical research to the benefit of man.

Along with monitoring of the environment for unacceptable types and levels of toxic substances, progress has also been made in the capability to monitor human populations. Epidemiologic data have provided clues to the cause of a disease, and have yielded decisive evidence of the effectiveness of particular prophylactic or preventive measures. Perhaps the most outstanding recent contribution from this field has been the linking of cigarette smoking with lung cancer, heart disease, and emphysema.

Population Problems

One major aspect of man's relation to his environment which increasingly engages medical science is the problem of

overpopulation. In many parts of the world the balance between numbers of people and availability of resources is in serious jeopardy. The problem is particularly severe in developing countries where population is rising faster than the food supplies, housing, manufactured goods, and services needed to improve the level of living. It is incumbent upon the technologically advanced nations to apply the necessary resources and scientific effort to the development of effective, acceptable means of contraception, in the interest of both individual and social health.

Research in endocrinology has resulted in development of the oral contraceptives, which have had a profound effect on family planning. The intrauterine device (IUD), introduced in the 1930's but soon abandoned, was reintroduced in modified form about mid-century as an effective family-planning device. Studies of the entire reproductive process will eventually lead to the development of contraceptive techniques that will be effective, safe, simple, easy to use, inexpensive, reversible, and acceptable to various population groups. The acceptance of family planning practices--the spacing of children--will improve maternal health. The improved health of the mother will in turn affect the quality of the offspring and reduce infant mortality and morbidity.

IMPEDIMENTS

Impediments that stand in the way of solving problems of disease warrant attention. Some constraints derive from essential characteristics of the scientific research process, others are clearly outside science, while another group is at the interface.

Constraints Essentially Scientific in Character

Of the limitations inherently scientific, two in particular deserve mention. These are the *problem of inadequate knowledge* and the *problem of inadequate methodology.*

The biomedical sciences, despite enormous progress, remain highly empirical. Elegant models and predictive theories--atomic structure models, quantum theory, relativity theory--which have played so important a role in organizing and advancing knowledge in the physical sciences, have few counterparts in the biological and medical sciences. Thus, the biomedical scientist must contend with large gaps in knowledge. Moreover, the lack of organizing principles and theories makes

it difficult both to characterize the nature of ignorance and to select systematic approaches to problems. Operationally, therefore, biomedical scientists must focus on emerging opportunities and tractable problems, on an essentially *ad hoc* basis. In the absence of good ideas and promising leads, neither fiats nor large financial investments are likely to result in much progress.

The problem of *inadequate methodology* is perennial; science is always limited by its methods. A hypothesis is useless unless it can be tested; instrumentation and procedures must be available to make observations that are (or are not) consistent with the hypothesis. Methodology and concept are profoundly interrelated in science, and without the former, conceptual advances are either impossible or vacuous.

The available methodology of biomedical science leaves much to be desired in respect to several general classes of problems. One of these might be termed *process dynamics*. Many biological processes advance so slowly and imperceptibly that precise measurement of either spontaneous or induced change over short epochs is not reliable. For example, it is very difficult to assess the progress of atherosclerosis and to determine whether experimental intervention has been effective. Another class of problems falls in the category of *superabundance of variables*. Even the best experimental

design in biomedical science may leave many variables beyond the control or even the awareness of the scientist. Thus, unambiguous answers to important questions of cause and effect must await the discovery of better approaches. A third class of problems derives from *small differences*. The measurement and interpretation of potentially important differences of small magnitude can be difficult: the random background variability, or "noise," must be separated from the "signal." This was not a consideration in testing the antimicrobial chemotherapeutic agents, first introduced with the sulfonomides in the 1930's and now including a long list of antibiotics, for these produce rapid and unambiguous results in the treatment of experimental or natural infections. But investigators are increasingly concerned with effects that are small; and the demonstration of significant differences depends on a large number of long-term observations. Examples would include studies on the toxicity of exogenous chemicals--a serious problem when great numbers of persons are exposed, as in the case of oral contraceptives, food additives, and contaminants of air, water, or food supplies.

Historically, there has been a dynamic interplay between measurement and conceptualization in science. One may hope that advances in methodology will overcome some of the problems of measurement which appear so formidable with presently available techniques and procedures.

Constraints in Part Scientific, in Part Nonscientific

Logically related to these scientific obstacles are impediments that contain important nonscientific elements. The *purview of biomedical science*, for one, may require respecification. It is often not a matter of clear consensus that a given problem related to health is scientific. Alcoholism, drug abuse, alienation--are these diseases? If so, to what extent does preventive intervention devolve upon health professionals, and what are proper limits on such intervention? Should the research efforts subtending such modes of intervention include research on methods to influence public policy and modify social forces? Accidents and self-destruction are the principal cause of death among teenagers and young adults, but medical science can do little for the youth whose chest is crushed and aorta ruptured in an automobile accident. What are the role and appropriate scope of medical research and preventive medicine in reducing mortality in such problem areas? There is a growing propensity to view an increasing range of phenomena as within the purview of biomedical science.

Risk/benefit considerations in clinical research and practice constitute another impediment. The management of health problems always involves studies on humans, for progress requires the introduction of new and better therapies. In

some instances, animal experimentation can provide much assurance that human trial is warranted, but its limitations are legion, and in any case, the really relevant subject is man. Thus, agonizing decisions on the extent to which biomedical scientists are justified in introducing novel interventions--which are both potentially risky and potentially beneficial--exert an important constraint on scientific solutions to health problems. One of the most poignant of these risk/benefit problems arises when a procedure or medication, long hallowed by conventional wisdom, comes under suspicion as either worthless or harmful and a scientist must design a study that withholds what is generally regarded as beneficial.

The problem of *technologic assessment* presents a third impediment. Any proposal for the introduction of a scientific or technologic advance should be preceded by a careful attempt to predict *all* major short- and long-range consequences. In the past, such efforts have not been highly successful. Few foresaw or early recognized the impact on ecosystems of phosphate detergents, insecticides, industrial waste. Yet today the world faces serious crises due to technologic innovations with obvious short-term advantages but with unanticipated, inexorably growing noxious consequences. Similarly, the long-range consequences of biomedical discovery have not always been systematically explored. Do we

fully apprehend all the consequences of eventually controlling major health problems--cancer, heart disease, stroke? To what extent should such understanding be pursued? What decisions might be appropriate, and for whom to make, as a result of the exercise?

Nonscientific Constraints

Two major constraints, essentially nonscientific, modulate the rate at which science can serve human health. The first of these is *economic;* the second, the *procedures for coupling* new knowledge to health care delivery.

The *economic* constraints are related to the fact that research, addressed to the creation of new knowledge--to the discovery of the unknown--is a high-risk venture with no guarantee of success. By transferring so much of the support of research to the public and especially to the Federal sector, society has spread broadly the risks as well as the benefits. The infrequency and unpredictability of major breakthroughs has focused serious attention and debate on the magnitude and character of support to be tendered the multiple research programs that fall within the purview of the Government. The methodologies of the social sciences are often unequal to answering the key questions. Economic analyses--cost/benefit studies, appraisals of returns on marginal investments,

estimates of opportunity costs, etc.--have been difficult to apply in a comprehensive and systematic way. In actual practice, decision-making in both the Exective and Legislative Branches has relied heavily on intuitive judgments both of a scientific-technical character and of a public-policy nature.

Thus, the major determinant of the national level of biomedical research, reflected in Executive acceptance of Congressional actions, is the national will. The citizenry of the country ultimately decides upon the intensity with which the problems of disease will be attached, the manpower and treasure that will be devoted to the effort, and the relative priority to be accorded health research versus other public and private purposes.

The second general area of nonscientific constraints might be called *coupling problems*. Knowledge of itself will not resolve the health problems facing mankind. New knowledge gained through research must be embodied in the technologic processes and systems through which health care is provided. Seminal research discoveries are seldom ready for application; once applicability is recognized, a stage of technological development, followed by a stage of careful testing (often under close supervision by a regulatory agency representing the interest of the general public), is usually required.

When these phases have been successfully completed, the new technology must be introduced, often under modulation by regulatory authorities, into institutional forms that operate in the society to provide health services. Health care delivery in the United States, predominantly conducted within the private sector, is highly decentralized and has a minimum of organization and structure. Under these circumstances, widespread acceptance and utilization of a new technology exacts a formidable effort from its proponents. Useful information is and will continue to be widely available, and methods for the dissemination of information are well advanced. The more critical problems remain--actual use of available data or widespread incorporation of technologic advances into the processes of health care delivery. Effective methods for accelerating solutions to this set of problems are not subject to clear consensus, a reality related to the private nature of the practice of the healing arts.

APPLICATION OF KNOWLEDGE TO HEALTH CARE

The nature and limitations of the health-care delivery system--and the opportunities it affords for improved application of new knowledge--warrant further elucidation.

Nature of the Health Care System

The health-care delivery system of the Nation contrasts in a number of particulars with that just described for the development of new biomedical knowledge. Apart from the enormous differences in scale (with health care expenditures 20 to 25 times those devoted to research), these contrasts are in such fundamentals as the relative homogeneity of the two systems, the extent to which identifiable authorities provide internal order or governance, the nature and degree of Federal involvement, and the relative stability of the systems from the point of view of public policy.

The system of delivery for health care in the United States has changed little over the past century. With modest

but increasing exceptions, it still adheres to the philosophy that medical care is a private matter. It follows essentially a fee-for-service concept, with a one-to-one relation between patient and physician. The providers of care, for the most part, have the right to select the individuals to whom they render care, and the consumer has the responsibility to pay for the care he receives.

The direct Federal role in health care--by contrast with its broad role in research--has been fairly limited to particular client groups, such as veterans, military personnel and their dependents, American Indians, and merchant seamen. These groups have been cared for in Government-operated subsystems, contiguous to but insulated from health care in the broader community. Apart from this concern for special groups, the Government has been mainly a final arbiter in the health care area, intervening only when help is sorely needed and the private market has been unable to cope with a particular problem.

Limitations of the System

One limitation of the existing health care arrangement has already been identified: the difficulty of assuring widespread adoption of scientific and technologic innovation into a system that is highly decentralized and has a minimum

of organization and structure. The most effective points for interchange between health research and health care are the teaching hospitals in leading medical centers. In such institutions, staff involvement in a combination of research, teaching, and health care does much to bring to patient needs a quality of attention seldom achieved in less-favored settings. Despite close coupling between research and care in certain institutions, the discontinuities in the health care system cause wide variation in the degree and timing of the public's enjoyment of research benefits. One important effort made by the Federal Government to reduce the impact of these discontinuities was the creation of the Regional Medical Programs in 1965.

While many points of excellence in the health care system may be identified, dissatisfaction with major aspects of that system has become pervasive. Many informed persons speak of a "health care crisis," with the quality of health care, its costs, its accessibility, and the financing arrangements for it all under serious challenge.

In the last twelve months alone, America's medical bill went up eleven percent, from $63 to $70 billion. In the last ten years, it has climbed 170 percent from the $26 billion level of 1960. Over the same period, the proportion of Gross

National Product spent on health has risen from 5.3 percent to 7 percent. Several factors have contributed to an escalation of total expenditures with little solid evidence of concomitant gain in the quality and quantity of health care actually delivered. One of these is an insurance system that encourages use of higher-cost hospital or in-patient care rather than less expensive out-patient or home care. Another factor has been major new Federal programs, such as Medicare and Medicaid, that have vastly increased the number of persons who can request and pay for the health care they would previously have received without cost or would have done without entirely. Meanwhile, these programs have done little to increase the available *resources* for providing care, and supply-demand factors have caused prices to rise.

Apparent shortages of health personnel may be observed in virtually all categories, including physicians, nurses, allied workers. The evidence is apparent--on at least an anecdotal basis--for almost anyone seeking urgent or emergency health care. Yet broad agreement on exact numbers of additional personnel needed in any of the various health categories is lacking. Would the present number of physicians suffice if more efficient forms of health care delivery--for example, group practice arrangements--were adopted? Is the problem principally one of maldistribution of personnel, either

geographically or in terms of specialities, rather than one of overall numbers? Such questions serve to illuminate the complexity of health personnel issues, without invalidating the commonsense observation that our present health care system is inadequately staffed.

Opportunities for Improved Application of Knowledge

Because of the Government's financial involvement and heavy burden of cost in health care delivery, there are important opportunities for structuring incentives and providing new directions for the system. The Government has already taken advantage of this opportunity by proposing to reorganize the delivery of services, to meet the needs of scarcity areas, to meet the personnel needs of our health care system, and to support programs of illness and accident prevention.

In respect to the first of these proposals--to reorganize the delivery of services--the Administration has offered to support a new approach to health care: the use of Health Maintenance Organizations (HMO's). Under this program, the Federal Government would require private and public health insurance carriers to allow beneficiaries to purchase membership in a Health Maintenance Organization when one is available, would support the establishment of HMO's, and would

propose model statutes to facilitate the development of HMO's in the States.

To meet the needs of scarcity areas, HMO's would be encouraged to locate in areas of medical scarcity; outpatient clinics would be supported in such areas; the medical system of the Veterans Administration would be developed to supplement local medical resources where needed; a series of Area Health Education Centers would be established; and physicians and nurses who practice in underserved areas would be rewarded.

To meet the personnel needs of our health care system, the proposals to encourage HMO's and to serve scarcity areas would seek to improve the effective use of existing medical manpower. But more health professionals must be produced. To this end, the Federal Government has proposed to emphasize new methods in support of medical education, to help low-income students enter medical and dental schools, and to support the wider use of allied health personnel.

The Federal Government has reaffirmed and expanded its commitment to biomedical research, acknowledging the basic and irreplaceable contribution of science to the delivery of health care.

OVERVIEW OF THE PAST AND OUTLOOK FOR THE FUTURE

The last century has witnessed a transformation unprecedented in human history--a reduction of the toll exacted from mankind by his ancient enemies, disease, disability, and premature death. This phenomenon was largely a result of the application of scientific knowledge to the problems of human health. During the last quarter century, the mobilization of science for the solution of health problems has been intensified as a consequence of the emergence of a broad national consensus that health is a desirable and attainable social objective. Paced by public funding, the level of effort of both basic and applied research in the biomedical sciences has grown, and fundamental science and clinical medicine, interacting, have enriched each other.

Even a brief catalog of achievements that have redounded to improvements in human health--such as this paper attempts under "Accomplishments"--cannot fail to convey the sense of great progress that has occurred, the excitement of the endeavor, and the dynamism of growth in knowledge. At the same

time, the rate of progress in solving health problems has been slowed by gaps in knowledge, by deficiencies of methodology, and by limitations such as risk/benefit considerations, inadequacy of resources, and inertia in coupling new knowledge and technology to clinical practice. To some extent at least, this inertia is attributable to the character of the American health-care delivery system--private, loosely organized, and entrepreneurial.

Scientific Problems and Opportunities

Despite impressive progress in understanding disease and improving the methods for preventing and treating it, there remain vast areas that continue to resist scientific penetration. Research is the one hope that man will extend his mastery to these.

The future is bright for further advances in biomedical science. While it is impossible to predict the nature or timing of such advances, a consensus that rapid progress is likely to occur soon in some areas frequently crystallizes within the scientific community. In other areas, past experience lends confidence that a continued mining will reveal new lodes of knowledge and more certain directions for achieving the goal of better health. Several areas in which rapid progress is anticipated can be identified.

Major advances in the understanding of cancer, as well as real progress in the management of patients with this complex group of diseases, have taken place in the last 25 years. Numerous research leads are ready for extension to additional kinds of causative agents and types of cancer and for development into means of prevention. Basic knowledge of the causation and therapy of various types of cancer is still lacking, but many scientists believe that the new insights into the role of nucleic acids in cell biology will eventually provide key information about the cancer process.

Continued accrual of knowledge on the relation of certain fatty substances in the blood to heart attacks and other circulatory diseases is forecast with some confidence. The precise identification of such relationships may lead to means for preventing the process that terminates in sudden fatal occlusion of the coronary artery and certain types of stroke.

In the offing too is a better prospect for the dental health of young people, through the elucidation of methods to control tooth decay and gum diseases. Dental caries is now known to be an infectious disease, caused by specific types of bacteria, and there is evidence of a similar factor in the causation of periodontal disease. Various antibacterial agents and new techniques for protecting teeth from destructive bacterial action are being vigorously explored.

Research in human genetics has revealed a number of opportunities for control of hereditary diseases; extension of methods for identifying carriers and for the prenatal diagnosis of afflicted individuals is likely. It may be possible in the future to repair the genetic defect by replacement of a missing gene, but such technology is far from developed.

Increased understanding of fundamental immunology can be expected to aid in the development of methods for the control of transplantation rejection phenomena, which are now managed with only partial success through use of drugs. These suppress the immune reaction generally and carry the danger of lowering the body's ability to cope with infection. What is needed is an ability to effect tolerance for the particular tissues to be transplanted. Additional basic knowledge of the immune mechanism will in all probability increase understanding of the so-called autoimmune diseases and some of the fatal collagen diseases. Recent elucidation of the role of measles virus in subacute sclerosing panencephalitis, a severe, progressive disease of the central nervous system, has revealed a possible immunologic component. Similar mechanisms are being studied in relation to the causation of other neurological diseases that appear to be associated with the "slow" viruses. Control of the immune process, as well as precise identification of the viral agent, may be the key

to the prevention of the inexorable deterioration in neurological function now associated with these afflications.

Continued efforts in biomedical research may also provide improved means of control over the human reproductive process. Research has recently been intensified on all aspects of the fertilization, transport, and implantation of the ovum in the uterine wall, and on subsequent developments, with a view to identifying stages in these processes which may be vulnerable to new contraceptive drugs. Work is also proceeding on means to control male fertility without harmful side effects.

Like most ventures into the unknown, biomedical research addressed to the creation of new knowledge offers no immediate guarantee of success. But if the past is prelude, then exploitation of the current research opportunities should eventually yield answers to what are now complex puzzles. These answers will surely help to augment the quality of health care and to improve human health and well-being.

Public Policy Problems and Opportunities

The central role of public agencies (principally Federal) in the support of health-related research will inevitably

thrust many issues, problems, and opportunities into the domain of public policy. Thus, they become matters for national discussion and debate and for resolution through national political processes. Among these matters, the following deserve attention.

Allocation of resources. Perhaps the most vital issue facing the Nation is the question of the quantity of national resources to be devoted to health. Within this general question exist equally difficult ones, such as the proportions of the health dollar to be allocated to biomedical research and to services. Public policy must be designed to obtain optimal balances between such alternatives as these: fundamental research with a long-term payoff as against research with more short-term benefits; support of research today versus investment for the future in resources such as manpower and facilities; and research in categorical diseases versus research in scientific disciplines which may lead to new knowledge applicable across disease categories. In the business community, such a strategy can be guided by the profit calculus; in the public sector, a viable strategy must recognize the whole gamut of economic and human values that society is seeking through health research. Once developed, the strategy will need to be adapted flexibly as unforeseen opportunities arise and the scope of research broadens.

A number of questions of great importance must be under continuous scrutiny, and periodic changes in policy may be necessitated by developments within science or external to it. One major problem is the *stabilization* of the national research effort--that is, the commitment to long-range plans which preclude abrupt variations in the national level of effort. Lacking a reasonably firm estimate of future investments, especially in fields where the processes for creating manpower and facilities are slow, a highly unstable system of research, oscillating erratically between feast and famine, is the likely result. As soon as this becomes apparent, sponsors of research will encounter great difficulty in finding individual or institutional performers.

Another challenging problem is the development of machinery for selecting areas for differential investment. At any moment, a wide span of viewpoints on the most promising scientific opportunities prevails within the scientific community; many groups of knowledgeable and articulate investigators can present cogent and persuasive cases for their candidate programs. Subsidiary issues relate to processes for resolving problems when scientific and public perception of need and opportunity are in conflict. For example, when the "relevance" of science--bacteriophage genetics in the early 1950's--is not apparent to the nonscientist, what mechanisms can be

employed to maintain public confidence and scientific progress? Another facet of this problem relates to the mechanisms for identifying fields ripe for organized attack, and then for organizing scientists (who are by nature disposed to operate as individuals or members of small teams) into the large, structured, and anonymous configurations of investigators required by the task.

Mechanisms of support. The national health-related research effort has been supported in the past from a variety of sources. About 65 percent of the funds have come from the Federal Government, through annual Congressional appropriations to Federal agencies after careful review within the budget process by both the Executive and Legislative Branches. Whether or not this should continue is an open question. If health research is an advance payment for future health services or a long-range expense of health care, a case could be made for support of health research (and for that matter, health-service manpower and facilities) through a surcharge on current health-care expenditures, placed in trust and distributed through appropriate mechanisms. Obviously, such a radical change would call for careful study and discussion.

Federal roles. The last 25 years have witnessed the brisk evolution of Federal roles in respect to health generally

and in all aspects of health research. Should the past policies and attitudes continue or are significant changes in order?

In the domain of research, should the Federal role be one of broad patronage, with support for the initiatives of both individual scientists and academic institutions, for the creation of trained manpower and special facilities, for the development of research resources, and for the direct purchase of specifically defined products and data under centrally managed contracts with industrial and academic performers? Or should there be a shift in policy, and if so, in what direction? Toward more or less support of the system for scientific re-research? Toward more or less direct purchase of the products of research? What broad principle should determine definition or redefinition of the Federal role in support of biomedical science?

Important facets of this issue relate to Federal roles in the support of training for research, of institutions engaged in research, and of direct research in Federal laboratories. The Federal role in the support of graduate education has been under intensive review for the last several years, on both pragmatic and ideological grounds. Highly trained manpower is undoubtedly required if the national research effort is to be sustained, if new blood is to be brought into graduate

faculties of universities, if competence in modern medical science is to be reflected in medical faculties. Are there better mechanisms for achieving these objectives? Is large-scale Federal assistance still necessary? If so, in what amounts?

What should the future Federal role be in respect to academic and nonacademic research institutions? What kind of stability do these institutions require, and how much of what kind of instability is necessary, tolerable, and desirable. What role, if any, has the Federal Government in the maintenance of institutional excellence and in the proliferation of excellent institutions. What role in the development of emerging institutions? In wider geographic dispersion of institutions committed to research and graduate education? What basic principles should guide the development of policy in this area?

Protection of privacy. Large-scale survey research and epidemiologic studies coupled with advanced technology promise exceptional opportunities for obtaining knowledge about the incidence, nature, prevalence, and causation of critical health problems. The national need for this information, however, must be somehow reconciled with constitutional guarantees affording an individual subject his right to privacy. How

can data bases essential for legitimate research be established and this right be simultaneously protected?

Risks and benefits of scientific innovation. Scientific experimentation in a free society frequently creates a dilemma. Often clinical trials of new methods for the treatment of human disease carry an expectation of great benefit to both the patient and society. On the other hand, a risk to the patient of unpredictable dimensions is always inherent in a new procedure. This type of problem constitutes a significant public policy issue for research administration and requires public decision for its resolution. Indeed, the issue becomes ever more critical as potentially useful experimental techniques proliferate.

Future Prospects

Thus, in looking ahead, it is clear that further improvements in the health of the Nation will be determined by the success with which a number of challenges are met by scientists and the body politic separately and together. Many problems in understanding and managing disease which, by present standards, appear intractable confront the scientific community. Yet the cascading discoveries of the recent past

have created many potentially productive leads as well as a widely shared sense of hope and optimism. The vigor, the context, the governance of the research enterprise will be determined to a large extent by our national purpose--by the values that the American people place upon health and by the acuity and force of their perception of the importance of research in the promotion of health and the control of disease. Together, a dedicated scientific community and an enlightened public, acting in mutually respectful cooperation, have it within their power to bring about a vast improvement in the health of mankind.